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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/IB97/01414 (22) International Filing Date: 29 October 1997 (29.10.97) (30) Priority Data: 96121322 31 October 1996 (31.10.96) RU (71) Applicant (for all designated States except US): AKTSION- ERNOE OBSHCHESTVO ZAKRYTOGO TIPA "OSTIM" [RU/RU]; Sechenovskiy per., 6-3, Moscow, 119034 (RU). (72) Inventors; and (75) Inventors/Applicants (for US only): RUDIN, Vsevolod Nikolaevich [RU/RU]; ul. Petrozavodskaya, 15-2-199, Moscow, 125502 (RU). BOZHEVOLNOV, Viktor Ev- genievich [RU/RU]; Bolshaya Kommunisticheskaya, 24/28-45, Moscow, 109004 (RU). ZUEV, Vladislav Petrovich [RU/RU]; ul. Tallinskaya, 2-316, Moscow, 123426 (RU). KOMAROV, Vladimir Fedorovich [RU/RU]; Shipilovskiy proezd, 53-15-606, Moscow, 115582 (RU). MELIKHOV, Igor Vitalievich [RU/RU]; ul. Krupskol, 19-55, Moscow, 117331 (RU). MINAEV, Vladimir Vasilievich [RU/RU]; Naberezhnaya Tarasa Shevchenko, 5-471, Moscow, 121248 (RU). ORLOV, Andrei Yurlevich [RU/RU]; ul. Kantimirovskaya, 12-1-471, Moscow, 121357 (RU).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: METHOD FOR PRODUCING A SUSPENSION OF HYDROXYLAPATITE (57) Abstract <p>The invention is concerned with an improved hydroxylapatite HAP composition in the form of a suspension or paste. The improvement is that the composition may have a homogeneous concentration in the range of from 7 % to 96 %. The invention is also concerned with a method for producing the homogeneous concentration compositions of HAP and their industrial applications.</p> 		

## METHOD FOR PRODUCING A SUSPENSION OF HYDROXYLAPATITE

Field of the invention

The present invention is concerned with a hydroxylapatite composition having a homogeneous concentration within the range of from 7 % to 96 %. The present invention also relates to a method for preparing the hydroxylapatite compositions and products containing the hydroxylapatite compositions and its use in specific applications.

Hydroxylapatite (HAP) may be used in medicine as a denture material, prophylactic additive in tooth pastes and medicinal solutions, chewing gums, sorbents for medicinal preparations and various organic and inorganic compounds, in materials for stomatology and bone surgery and as a filler or sorbent agent for gas-liquid chromatography.

State of the Art

Due to the fields of application of hydroxylapatite the availability of pure HAP, free from other calcium phosphates has become the main requirement. Furthermore, it became highly desirable to prepare HAP not only in powder form but as a suspension or paste of a predetermined composition.

A known method for producing hydroxylapatite is based on the mixing of a suspension of calcium hydroxyde with an aqueous solution of phosphoric acid, wherein either the reaction product of both components or the mixture is treated by a grinding operation that ensures a mechano-chemical activation of the reagents. According to this method as a grinding apparatus there may be used mills and crushers of various types and as a

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A disadvantage of this known method, however, is that a suspension with homogeneous concentration can not be obtained.

The preparation of highly concentrated suspensions of more than 18 % is time-consuming, requires large volumes of apparatus and the production of a suspension with a concentration higher than 33 % is practically impossible.

#### Description of the invention

The present invention is based on the problem to produce a suspension of hydroxylapatite with any necessary concentration, i.e. either less than 18 % or more than 33 % and as well pastes of hydroxylapatite having a homogeneous concentration composition.

According to the present invention a hydroxylapatite (HAP) composition is provided, wherein the dimensions of the hydroxylapatite particles is 0.01  $\mu\text{m}$  to 0.02  $\mu\text{m}$  in width and 0.5  $\mu\text{m}$  to 0.1  $\mu\text{m}$  length, the composition having a homogeneous concentration within the range of from 7 % to 96 %.

Preferred concentration ranges are given in subclaims 2 to 6. The composition may be in the form of a suspension or paste.

The hydroxylapatite (HAP) compositions of this invention are starting from a suspension of hydroxylapatite with a concentration of 4.5 % to 5.0 % which may be obtained preferably according to the method of the patent of the Russian Federation mentioned above. According to the invention such a suspension is subjected to alternating stirring and filtration ranges with the stirring being carried out at a rate of 0.8 m/s to 3.0 m/s for 5 to 25 minutes and each stage is providing increasing homogeneous concentrations of hydroxylapatite due to increased stirring rates and/or times. Thus, suspensions with concentrations of 7 % to 20 % in a first step, 21 % to 34 % in a second step, 35 % to 45 % in a third step, 46 % to 62 % in a fourth step, 63 % to 75 % in a fifth step can be obtained. The yield of the final pro-

sity and duration of stirring a partial or complete destruction of its structure occurs along with the transition of the sol into a gel. A subsequent filtration of the hydrogel results in a partial separation of the solvent (water) thereby concentrating the disperse system up to 7 % to 20 % and in the transition of the gel into a sol which has a spatial structure and stability formed at the expense of cohesion and aggregation of particles of the disperse phase, preventing its further filtration and concentration.

During further stirring the formed stable spatial structure depending on the intensity and duration of stirring is again partially or completely destroyed with the formation of a gel. The subsequent filtration of the hydrogel results in a partial and controlled separation of water, in concentrating the disperse system up to a concentration of 21 % to 34 % and the transition of the gel into a spatially structured and stable sol that practically prevents its further filtration and concentration. The same process occurs in all the subsequent stages of concentrating the suspension. The number of stages varies depending on the necessity to produce a suspension of a predetermined and required concentration.

From the above it can be seen, that the concentration of a suspension is a determining fact at each stage of the process. To adjust a desired concentration it is necessary to set specific conditions at the stage of stirring, e.g. rate and time, that in turn will depend on the type of the apparatus used, e.g. a tank with agitator, vibratory mill, vibrators with variable repetition and amplitude and so on and its volume. These parameters are selected in each case to produce a suspension of the desired concentration.

The method is illustrated by the following example(s).

#### Example 1

554.6 g of anhydrous calcium oxide are introduced into a reactor

based on the solid phase content in %, No. is the sample number and YP is the yield of the final product at the specified stage of the suspension processing.

The range of the agitation rate is determined by the aggregation degree of a suspension and by its concentration. At agitating rates lower than 0,8 m/s the sol destruction practically does not occur, even for suspensions of an initial concentration of 4 % to 5 % of HAP. At rates above 3.0 m/s the capturing of air bubbles and aeration of the suspension deteriorating of the product quality occurs requiring additional operations to expel them.

The present invention allows to provide suspensions (pastes) of hydroxylapatite having a composition that is determined by the field of their application. Suspensions (pastes) of hydroxylapatite possess an improved quality. A selection of the product at any stage allows to produce suspensions or pastes in a wide range of concentrations from 7 % to 96 %, the produced pastes having a homogeneous composition that provides substantially easy conditions for their application and handling.

subjected to alternating stirring and filtration stages with the stirring being carried out at a rate of from 0,8 m/s to 3,0 m/s for 5 min to 25 min, each stage thereby providing increasing homogeneous concentrations of HAP due to increasing stirring rates and/or times.

10. A denture material containing as a component a hydroxylapatite composition of claims 1 to 8 or obtained by the method of claim 9.

11. A tooth paste containing as a component a hydroxylapatite composition of claims 1 to 8 or obtained by the method of claim 9.

12. A chewing gum containing as a component a hydroxylapatite composition of claims 1 to 8 or obtained by the method of claim 9.

13. A sorbent material for gas-liquid chromatography consisting of a hydroxylapatite composition of claims 1 to 8 or obtained by the method of claim 9.

14. Use of a composition of claims 1 to 8 or obtained by the method of claim 9 for providing a preparation to be used in the field of stomatology.

15. Use of a composition of claims 1 to 8 or obtained by the method of claim 9 for providing a preparation to be used in bone surgery.

# INTERNATIONAL SEARCH REPORT

International Application No.

IB 97/01414

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C01B25/32 B01J20/04 G01N30/48 A61K6/033 A61L27/00  
A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C01B B01J G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 0 664 133 A (AKTSIONERNOE OBSHESTVO ZAKRYT) 26 July 1995 see the whole document ---	1-4, 14, 15
X	EP 0 261 458 A (TOA NENRYO KOGYO KK) 30 March 1988 see the whole document ---	1-5, 13
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A	US 3 873 327 A (DUFF EDWARD JOHN) 25 March 1975 see the whole document ---	10
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Date of the actual completion of the international search

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Information on patent family members

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